Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study

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Abstract

***Objective*—To study the correlation of antimicrobial consumption with the carriage rate of penicillin resistant and multiresistant pneumococci in children.**

***Design*—Cross sectional and analytical prevalence study.**

***Setting*—Five different communities in Iceland.**

***Main outcome measure*—Prevalence of nasopharyngeal carriage of penicillin resistant pneumococci in children aged under 7 years in relation to antibiotic use as determined by information from parents, patient's records, and total sales of antimicrobials from local pharmacies in four study areas.**

***Results*—Total antimicrobial sales for children (6223 prescriptions) among the four areas for which data were available ranged from 9.6 to 23.2 defined daily doses per 1000 children daily (1.1 to 2.6 courses yearly per child). Children under 2 consumed twice as much as 2-6 year olds (20.5 *v* 10.9 defined daily doses per 1000 children daily). Nasopharyngeal specimens were obtained from 919 children, representing 15-38% of the peer population groups in the different areas. Pneumococci were carried by 484 (52.7%) of the children, 47 (9.7%) of the isolates being resistant to penicillin or multiresistant. By multivariate analysis age (<2 years), area (highest antimicrobial consumption), and individual use of antimicrobials significantly influenced the odds of carrying penicillin resistant pneumococci. By univariate analysis, recent antimicrobial use (two to seven weeks) and use of co-trimoxazole were also significantly associated with carriage of penicillin resistant pneumococci.**

***Conclusions*—Antimicrobial use, with regard to both individual use and total antimicrobial consumption in the community, is strongly associated with nasopharyngeal carriage of penicillin resistant pneumococci in children. Control measures to reduce the prevalence of penicillin resistant pneumococci should include reducing the use of antimicrobials in community health care.**

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Introduction

Bacterial resistance to antimicrobial agents is a rapidly increasing problem worldwide. The first strains of pneumococci resistant to penicillin (minimal inhibitory concentration >0.1 mg/l) were isolated in the mid-1960s.[1] Subsequently, resistant isolates have been reported with increasing frequency from all parts of the world but the prevalence has remained low in northern Europe.[1-5]

In Iceland the first penicillin resistant pneumococcus was isolated in 1988. By 1993 about one fifth of pneumococcal strains isolated from infected patients were resistant to penicillin.[6 7] Most of the penicillin resistant pneumococci isolated in Iceland (around 80%) are multiresistant—that is, resistant to penicillin, ampicillin, cephalothin, erythromycin, clindamycin, tetracycline, fucidic acid, sulphonamides, and trimethoprim. These multiresistant strains are of serotype 6B and probably belong to a single clone originating from Spain.[8]

Consumption of antimicrobials is a major factor contributing to resistance in hospitals.[9] The relation between antimicrobial consumption and resistance in the community has been less thoroughly studied.[10 11] Little is known about the impact of different classes of antimicrobials on the spread of resistant strains by selective pressure.

Antimicrobial consumption is higher in Iceland than in other Nordic countries.[12] We aimed at analysing the correlation of nasopharyngeal carriage of penicillin resistant pneumococci with antimicrobial use in children in different communities in Iceland with regard to both individual use and total use among these children.

Population and methods

TARGET POPULATION

At the end of 1993 the population of Iceland was 264 919. Five geographical areas were chosen (fig 1) which had a total population of 37 732. The five areas were Hafnarfjördur-Gardabaer (HG), Vestmannaeyjar (V), Egilsstadir (E), Bolungarvik (B), and Hella-Hvolsvöllur (HH). The population of the five areas included 4718 children aged under 7. Children are eligible to attend public day care centres from 2 years of age. Younger children are commonly looked after in private day care centres or in small groups by child minders.

ANTIMICROBIAL SALES STATISTICS

Computerised information on total sales of antimicrobials prescribed for adults and children was collected from the local pharmacies in four areas (HG, V, E, and B; data not available from area HH) for the period October 1992 to September 1993 inclusive. Numbers of defined daily doses[13] were calculated per 1000 population per day and for different age groups.

SELECTION AND RECRUITMENT

Nasopharyngeal specimens were collected during October 1992 to November 1993 inclusive (but excluding June, July, and August). Each child was entered only once, children who had received an antimicrobial agent in the preceding two weeks being excluded. On given days we visited day care centres and collected specimens from all children present. Similarly, when time allowed, children attending the health care centres for vaccinations or because of acute upper respiratory tract infections were consecutively recruited. Informed parental consent was obtained in all cases.

Table 1—*Antimicrobial sales statistics for children aged <7 years in four study areas (October 1992 to September 1993 inclusive)*

Study area	Population	Yearly courses per child	No of defined daily doses per 1000 children				
			Total	Phenoxymethylpenicillin	Aminopenicillin ± clavulanic acid	Co-trimoxazole	Erythromycin
HG	3204	1.2	11.9	2.2	7.0	2.2	0.5
V	635	2.6	23.2	3.5	9.7	7.1	2.9
E	382	1.4	13.4	2.4	7.0	3.5	0.5
B	147	1.1	9.6	2.5	4.3	2.2	0.6

By means of a questionnaire the following information was collected from general practitioners' records or from the parents when their children were seen by other professionals (around 5% of cases): number of antimicrobial courses in the preceding year; date and name of the last antimicrobial agent; type of infection; and whether the child had been taking prophylactic antimicrobials for three weeks or more in the preceding year. The study was approved by the ethics committee of the director of public health.

MICROBIOLOGY

Nasopharyngeal samples were obtained with a rayon tipped swab (Mini-tip Culturette; Becton Dickinson and Co, Maryland, USA), stored for maximum of 48 hours until processing in the microbiology laboratory at Borgarspitalinn, then inoculated on to blood and chocolate-blood agar (Difco, Detroit, Michigan) and incubated aerobically and anaerobically. Colonies were identified by conventional methods and susceptibility to tetracycline, erythromycin, chloramphenicol, sulphonamides, and trimethoprim tested by the Kirby-Bauer method.[14 15] Pneumococci were screened for penicillin resistance by the oxacillin disc diffusion test[16] and the minimal inhibitory concentration of resistant isolates determined by the agar dilution method.[15] Isolates of pneumococci with a minimal inhibitory concentration of penicillin exceeding 0.1 mg/l were considered resistant. The serotype of the resistant isolates was determined by coagglutination[17] with antisera from the Statens Seruminstitut, Copenhagen. Serotyping and minimal inhibitory concentration determinations were performed by the microbiology department at Landspitalinn.

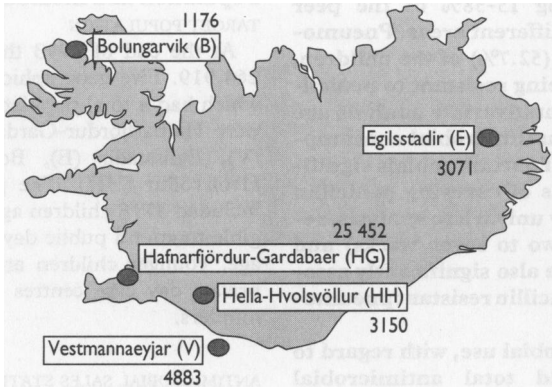

Fig 1—*Location of five study areas in Iceland and numbers of inhabitants*

Table 2—*Nasopharyngeal culture population by study area and sampling group*

Study area	Population studied (mean age in years)	Percentage of total population aged <7 years	No recruited from health and day care centres† (mean age in years)	No with upper respiratory tract infection (mean age in years)
HG	586 (3.3)	18	339 (3.8)	247 (2.7)
V	100 (4.5)	16	100 (4.5)	
E	126 (3.4)	35	106 (3.7)	20 (1.5)
B	53 (3.8)	38	53 (3.8)	
HH	54 (2.6)	15	5 (3.7)	49 (2.5)
Total	919 (3.4)	20	603 (3.9)	316 (2.6)

†491 Children (mean age 4.3 years) were recruited from 12 day care centres (mean of 63% of day care children participated in study).

STATISTICAL ANALYSIS

The single outcome variable was carriage of penicillin resistant pneumococci or carriage of penicillin sensitive pneumococci. The variables sex; age (<2, 2-3, and 4-6 years); area of residence; whether there were siblings; whether attending day care; presence or absence of an upper respiratory tract infection at the time of investigation; and the last antimicrobial agent used and number of courses (none, 1 or 2, or ≥3) in the preceding 12 months were examined for their association with the outcome variable. Multivariate logistic regression was used to estimate the odds of carrying penicillin resistant pneumococci to control confounding for interdependence. We could not include weeks from last treatment in the same multivariate logistic model because of the strong relation with number of antimicrobial courses.

All scientifically relevant variables were included in the multivariate logistic models irrespective of their contribution. The rationale was to provide as complete control of confounding as possible within the dataset.[18] It is possible for individual variables not to exhibit strong confounding, but when variables are taken collectively considerable confounding can be present.[19]

Individual regression coefficients were tested with the Wald statistic and confidence intervals calculated for the odds ratios. Multivariate analyses were performed with SPSS for Windows, Advanced Statistics Release 6.0 (SPSS Inc, Chicago). Univariate analysis of categorical variables was by χ^2 test. The level of statistical significance was taken as 0.05.

Results

ANTIMICROBIAL SALES STATISTICS

A total of 22 132 antimicrobial prescriptions were dispensed by local pharmacies in the four study areas for which information was available, corresponding to 13.6 defined daily doses per 1000 inhabitants daily in area HG, 19.9 in area V, 16.7 in area E, and 13.6 in area B. Of these prescriptions, 6223 (28.1%) were for children under 7. Children under 2 years consumed 20.5 defined daily doses per 1000 daily whereas 2-6 year olds consumed only half that (10.9). Children in area V consumed about twice the amount consumed by children in other areas and most of the co-trimoxazole and erythromycin (table 1).

NASOPHARYNGEAL CARRIAGE

Nasopharyngeal specimens were obtained from 919 children (table 2). Of these, 484 (52.7%) carried

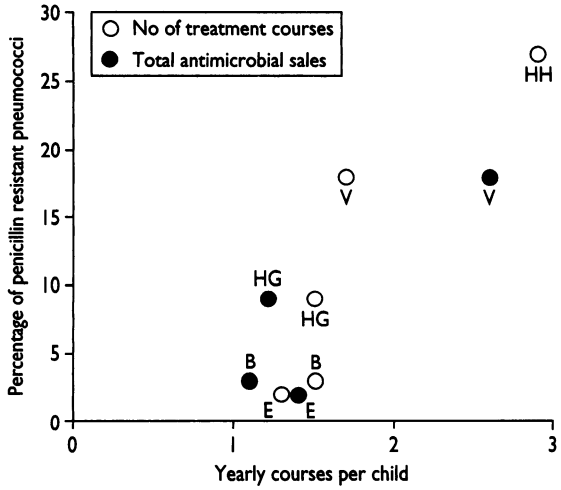

Fig 2—*Association between carriage rate of penicillin resistant pneumococci and antimicrobial consumption as determined from patients' records or questionnaires† (numbers of treatment courses) and total antimicrobial sales (calculated as numbers of treatment courses in target populations aged <7 years) in the study areas.*
†Mean age of sampling groups was lowest in area HH (2.6 years) and highest in area V (4.5 years).

pneumococci in the nasopharynx (table 3). In 15 instances the parent or child refused sampling.

Forty seven (9.7%) of the pneumococcal isolates were penicillin resistant (table 3). Of these, 43 were multiresistant strains of serogroup 6, two were strains of serogroup 19 (also resistant to trimethoprim and sulphonamides), and two were strains of serogroup 23 (both also resistant to trimethoprim and sulphonamides, and one resistant to tetracycline). The penicillin minimal inhibitory concentration of the serogroup 6 strains was 1.0 mg/l for 30 strains, 2.0 mg/l for 10 strains, and 0.5 mg/l for three strains. The serogroup 23 strains had minimal inhibitory concentrations of 0.125 and 0.25 mg/l and the serogroup 19 strains minimal inhibitory concentrations of 0.125 and 1.0 mg/l. Multiresistant pneumococci were found in all study areas.

ANTIMICROBIAL USE

Information about antimicrobial usage during the 12 months before the investigation was obtained for 887 children. Of these, 580 (65.4%) had received an antimicrobial agent at least once, the main indication (377 cases; 65.0%) being acute otitis media. Table 4 lists the use of the different antimicrobial classes.

FACTORS ASSOCIATED WITH CARRIAGE OF PENICILLIN RESISTANT PNEUMOCOCCI

By multivariate analysis three variables—age under 2 years, residence in area V, and individual use of antimicrobials—significantly influenced the odds of carrying penicillin resistant pneumococci (table 4). Gender, siblings, day care, antibiotics given as prophylaxis, and presence of an upper respiratory tract infection did not influence the odds.

Age—Twenty per cent (23/114) of pneumococci isolated from children under 2 were penicillin resistant as compared with 6.5% (24/370) of pneumococci from 2-6 year olds (P<0.001) (table 3).

Residence—Only residence in area V was significantly associated with higher odds of carrying penicillin resistant pneumococci (table 4). Sales of antimicrobials were also highest in area V (table 1). Figure 2 shows the association between the carriage rate of penicillin resistant pneumococci in each study area and antimicrobial consumption as determined from patients' records or questionnaires and sales figures from pharmacies.

Use of antimicrobials—Of the 167 pneumococcal carriers who had not received antimicrobials in the preceding year, only three (1.8%) carried penicillin resistant pneumococci. By contrast, of the 317 children who had received antimicrobials in the preceding year, 44 (13.9%) carried penicillin resistant pneumococci (P<0.001).

The carriage rate of penicillin resistant pneumococci was also associated with elapsed time since the last course of antimicrobials (fig 3). Children carrying penicillin resistant pneumococci who had been treated with antimicrobials in the preceding year were significantly more likely to have used antimicrobials within two to

Table 3—*Numbers of children carrying penicillin sensitive and penicillin resistant pneumococci by study area and age*

Study area	Children aged <2 years			Children aged 2-6 years		
	No	Penicillin sensitive	Penicillin resistant	No	Penicillin sensitive	Penicillin resistant
HG	174	70	17	412	209	11
V				100	45	10
E	34	10	1	92	46	0
B	7	2	1	46	36	0
HH	23	9	4	31	10	3
Total	238	91	23	681	346	24

Table 4—*Odds ratio of carrying penicillin resistant pneumococci as opposed to penicillin sensitive pneumococci by multivariate analysis (448 cases analysed, data missing in 36 cases)*

Variable	No	Odds ratio	95% Confidence interval	P value
Sex				
Male	224	1		
Female	224	1.06	0.54 to 2.07	0.858
Age (years)				
<2	109	1		
2-3	155	0.29	0.11 to 0.76	0.012
4-6	184	0.27	0.10 to 0.86	0.026
Study area				
E	54	1		
B	37	2.05	0.11 to 36.66	0.627
HG	279	5.33	0.67 to 42.74	0.115
HH	26	7.85	0.77 to 79.53	0.081
V	52	20.28	2.19 to 187.43	0.008
Siblings				
None	97	1		
≥1	351	0.84	0.38 to 1.85	0.669
Day care				
None	83	1		
Yes	365	0.76	0.30 to 1.86	0.548
Upper respiratory tract infection				
No	314	1		
Yes	134	1.14	0.47 to 2.75	0.774
Prophylactic antimicrobials				
None	433	1		
Yes	15	2.60	0.69 to 9.79	0.157
Type of last antimicrobial used and No of antimicrobial courses in past 12 months				
None	164	1		
β Lactam, 1 or 2	111	6.75	1.78 to 25.51	0.005
β Lactam, ≥3	54	6.00	1.44 to 24.77	0.013
Co-trimoxazole, 1 or 2	54	7.22	1.73 to 30.05	0.007
Co-trimoxazole, ≥3	42	13.14	3.15 to 54.86	0.000
Erythromycin, 1 or 2	11	8.56	1.14 to 64.04	0.037
Erythromycin, ≥3	12	12.16	1.96 to 75.36	0.007

Overall significance: $\chi^2 = 61.61$, df = 17, P<0.001.

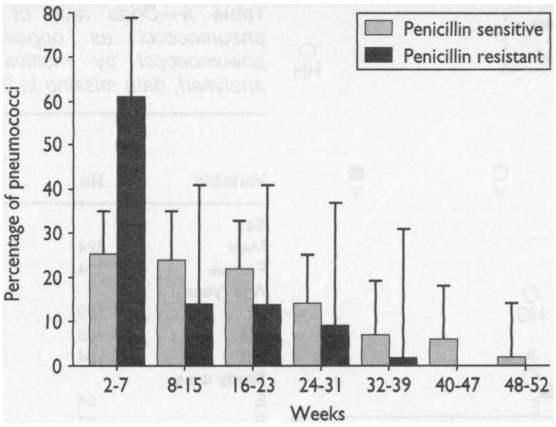

Fig 3—*Percentages of penicillin sensitive and penicillin resistant pneumococci by weeks since last antimicrobial treatment in children carrying pneumococci and having received antimicrobials in preceding year (311 children; data missing in six cases). Bars are 95% confidence intervals*

seven weeks than children carrying penicillin sensitive pneumococci (27/44 *v* 68/267; P<0.001).

Children carrying penicillin resistant pneumococci had received co-trimoxazole as their most recent antimicrobial twice as often (19/47) as children carrying penicillin sensitive pneumococci (79/420; P<0.001). This difference was not significant for other antimicrobials. By using the interaction between the last antimicrobial agent consumed and the number of antimicrobial courses in the multivariate analysis we found that the odds for co-trimoxazole and erythromycin being associated with carriage of penicillin resistant pneumococci were twice that for β lactams in association with three or more antimicrobial courses (table 4). Similar odds were observed when number of weeks since last antimicrobial treatment was entered into the model in association with two to seven weeks since last antimicrobial treatment instead of number of courses.

Discussion

A causal relation between antibiotic usage and resistance in hospitals has been established on the basis of consistent associations of the emergence of resistant strains with concurrent variations in use in populations over time.[9 20-22] Outside hospital the relation between antimicrobial use and the prevalence of β lactamase producing bacteria has been reported in children in day care,[11] but information on the major factors contributing to antimicrobial resistance in the community is less clear. Our study is one of the first to show clearly the association of antimicrobial use with antimicrobial resistance patterns in different communities.

The highest rate of penicillin resistance was in pneumococci carried by children aged under 2 (20%). This may be due to the fact that most of the penicillin resistant pneumococci were of serogroup 6, one of the most common serogroups carried by the youngest children.[23 24]

Children who had received antibiotics were significantly more likely than other children to carry penicillin resistant pneumococci, especially if the treatment was recent. Antimicrobials may eradicate sensitive organisms from the nasopharyngeal flora and so facilitate the establishment of a resistant strain. Furthermore, repeated antimicrobial courses may prevent spontaneous resolution of the penicillin resistant pneumococcal carrier state by virtue of their intermittent pressure.

By multivariate analysis no single antimicrobial class could conclusively be shown to be more definitively associated with carriage of penicillin resistant pneumococci. However, some treatment groups were small. Our data suggest that some agents may be more active in inducing a penicillin resistant pneumococcal carrier state because of selective antimicrobial pressure. For example, by univariate analysis only co-trimoxazole was significantly associated with carriage of penicillin resistant pneumococci. Children in area V had significantly higher odds than other children of carrying penicillin resistant pneumococci, and the most likely explanation was a much higher total use of antimicrobials, especially co-trimoxazole and erythromycin.

Geographical differences in antibiotic consumption have been noted in other Nordic countries,[11 25] but the explanation is not clear. In this study most antimicrobial prescriptions (65%) were for otitis media and geographical differences were likely to represent variations in prescribing habits rather than variations in the epidemiology of common childhood illnesses or the age profile of the population.

Recent studies have detected a high prevalence of penicillin resistant pneumococci in children attending some day care centres.[7 26] We, however, did not find attendance at day care to be an independent risk factor for carriage of penicillin resistant pneumococci, though this risk was difficult to assess because most children (around 80%) attended these centres.

We conclude that carriage of penicillin resistant pneumococci is strongly associated with the use of antimicrobials in the community. Both the public and professionals should be better informed about curtailing the misuse of antimicrobials in order to prevent or reduce the spread of penicillin resistant and multiresistant pneumococci, especially in children.

Key messages

- Evidence for the association between antimicrobial consumption in the community and the development of resistance has been poor, though the relation is well known in hospitals
- Study of the carriage of penicillin resistant pneumococci in 919 children in five different communities clearly showed the association of antimicrobial use with the level of resistance
- Repeated antimicrobial treatment courses and selective antimicrobial pressure may be particular risks for carrying resistant pneumococci
- Reducing the usage of antimicrobials, especially in children, is likely to be effective in preventing or reducing the spread of penicillin resistant and multiresistant pneumococci

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Case-control study of risk of dehydrating diarrhoea in infants in vulnerable period after full weaning

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Abstract

***Objectives*—To investigate risk factors for dehydrating diarrhoea in infants, with special interest in the weaning period.**

***Design*—Case-control study.**

***Setting*—Metropolitan area of Porto Alegre, Brazil.**

***Subjects*—Cases were 192 children aged 0-23 months hospitalised with acute diarrhoea and moderate to severe dehydration. Controls were 192 children matched for age and neighbourhood who did not have diarrhoea in the previous week.**

***Main outcome measures*—Associations between dehydrating diarrhoea and child's age, type of milk consumed, time since breast feeding stopped, and breast feeding status.**

***Results*—In infants aged <12 months the risk of dehydrating diarrhoea was significantly higher in the first 9 months of life (P<0.001), and in those aged 12-23 months the risk was again greater in younger children (12-17 months) (P = 0.03). The type of milk consumed before start of diarrhoea episode was strongly associated with dehydration independent of socioeconomic, environmental, maternal reproductive, demographic, and health services factors. Compared with infants exclusively breast fed, bottle fed infants were at higher risk (odds ratio (95% confidence interval) for cow's milk 6.0 (1.8 to 19.8), for formula milk 6.9 (1.4 to 33.3)). Compared with those still breast feeding, children who stopped in the previous two months were more likely to develop dehydrating diarrhoea (odds ratio 8.4 (2.4 to 29.6)). This risk decreased with time since breast feeding stopped.**

***Conclusion*—These results confirm the protective effect of breast feeding and suggest there is a vulnerable period soon after breast feeding is stopped, which may be of relevance for developing preventive strategies.**

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Introduction

Diarrhoea is still an important cause of death among young children in developing countries. Combinations of exposure to environmental pathogens, inappropriate diet, and malnutrition contribute to morbidity and mortality from diarrhoea. There may be up to 1000 million episodes of diarrhoea each year, of which about 2-3% may lead to life threatening dehydration.[1]

Poverty, lack of safe water and sanitation, early motherhood, and inadequate health care have been associated with a poor prognosis for diarrhoea among young children.[2] Lack of breast feeding also increases the risk of diarrhoea mortality.[3 4] In an earlier Brazilian study completely weaned infants had 14.2 times the risk of death from diarrhoea compared with breast feeding infants.[3] This protection can be explained by the anti-infective properties of breast milk, lower exposure to contaminated food and water, and improved nutritional status.[5 6]

The advantages of breast feeding have been highlighted by the World Health Organisation, which recommends that infants be fed exclusively with breast milk for the first 4-6 months.[7] In many countries, however, breast feeding is seldom exclusive and is of short duration.[8] In Brazil, for example, the median duration was 90 days among mothers of low socioeconomic status.[9] The intrinsic properties of breast milk suggest that protection is directly related to its presence in the diet.[5 10] No study, however, has attempted to assess whether the protection afforded by breast feeding against dehydration ceases immediately after full weaning or whether there is a carry over effect.

In this report we describe the results of our case-control study of dehydrating diarrhoea, with special emphasis on risk factors related to the weaning period.

Subjects and methods

The study was carried out in the metropolitan area of Porto Alegre (about 2.5 million inhabitants), in southern Brazil. Cases were children hospitalised with dehydrating diarrhoea, aged 0-23 months. They were enrolled from the two largest paediatric hospitals during the summer diarrhoea season, from December 1987 to April 1988. The eligibility criteria included a diarrhoea episode lasting less than eight days and the presence of moderate or severe dehydration—identified by a persistent skin fold plus at least one of the following signs: sunken fontanelle, dry mouth and tongue, sunken eyes, reduced urinary output, weak pulse, and irritable or sleepy condition. Physical examination was carried out by a trained paediatrician using a standardised protocol.